Part IV

Hemostasis and Disorders of Coagulation

WORD KEY

Anticoagulant • Delaying or preventing blood coagulation

Fibronectin • Protein involved in wound healing and cell adhesion

Lumen • Space within an artery, vein, or intestine or tube

Morbidity • State of being diseased

Mortality • Death

Polymerize • Process by which a simple chemical substance or substances are changed into a substance of a much higher molecular weight but with the same proportions

Thrombolysis • Breaking up of a clot

Transaminase • Aminotransferase (an enzyme)

Vasoconstriction • Decrease in the diameter of the blood vessels that decreases the blood flow

Viscosity • State of being sticky or gummy

Atresia • As in biliary atresia, congenital closure, or absence of some or all of the major bile ducts

Crohn's disease • Inflammatory bowel disease marked by patchy areas of inflammation from the mouth to the anus

Hemarthrosis • Bloody effusion inside the joint

Hematoma • Swelling composed of a mass of clotted blood confined to an organ, tissue, or space or caused by a break in the blood vessel

Keloid • Scar that forms at the site of injury that appears to have a rubbery consistency and shiny surface

Porcine • Of or relating to swine (pigs)

Consanguinity • Relationships among close blood relatives

Cryoprecipitate • Product derived from fresh frozen plasma that is rich in factor VIII, von Willebrand factor, and fibrinogen

Cytotoxic • Antibody or toxin that attacks the cells of particular organs

Hemangiomas • Benign tumor of dilated blood vessels

HLA • Human leukocyte antigens, which are found in white blood cells and are part of the major histocompatibility complex

Hyperviscosity • Excessive resistance to the flow of liquids

Menorrhagia • Excessive menstrual bleeding

Microangiopathic • Related to pathology of small blood vessels

Paresthesias • Abnormal sensation that results from an injury to one or more nerves, described as numbness or prickly or tingling feeling

Telangiectasia • Vascular lesion formed by dilation of a group of small blood vessels, most frequently seen on face and thighs

Alloimmunization • Antibodies that occur as a result of antigens introduced to the body through blood and tissue

WORD KEY

Acrocyanosis • Blue or purple mottled discoloration of the extremities, especially the fingers, toes, and nose

Immunologic assay • Measuring the protein and protein-bound molecules that are concerned with the reaction of the antigen with its specific antibody

Monoclonal • Arising from a single cell

Recombinant • In genetic and molecular biology, pertaining to genetic material combined from different sources

Reptilase time • Coagulation procedure similar to thrombin time except that the clotting is initiated by reptilase, a snake venom; using reptilase, heparin will not affect the assay

Thrombin time • Using thrombin as a substrate, this assay measures the time it takes for fibrinogen to be converted to fibrin

Thrombolytic therapy • Using an agent that causes the breakup of clots

Angina • Oppressive pain or pressure in the chest caused by inadequate blood flow and oxygenation to the heart muscle

Atherosclerosis • Cholesterol-lipid-calcium deposits in the walls of arteries

Fibrillation • Usually refers to a cardiac fluttering due to faulty electric supply to the heart

Gangrene • Death of tissue usually resulting from deficient or absent blood supply

Necrosis • Death of cells, tissue, or organs

Purpura fulminans • Rapidly progressing form of purpura occurring principally in children; of short duration and frequently fatal

Vasculitis • Inflammation of the blood vessels.

Venogram • Radiograph of the veins

COMPONENTS OF THE HEMOSTATIC SYSTEM

Components of the global hemostatic system include

- Platelets
- von Willebrand's factor (vWF)
- Tissue factor, which has a critical role in initiating the coagulation cascade
- Clotting factors (proteins of the coagulation cascade)
- The fibrinolytic system (plasminogen/plasmin, tissue plasminogen activator)
- Anticoagulant proteins (antithrombin, protein C, protein S)
- Endothelial cells, which have an active role in preventing thrombosis

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- **Primary Hemostasis**
  -Platelet plug formation
- **Secondary Hemostasis**
  -Procoagulant protein cascade
- **Anticoagulant balance and remodelling**
  -Natural anticoagulant proteins
  -Fibrinolysis

ENDOTHELIAL CELLS IN HEMOSTASIS

Endothelial cells are not passive blood vessel wall linings; they are active participants in global hemostasis. Endothelial cells are particularly important in the *prevention* of coagulation.

- **Endothelial cell surface molecules:** Endothelial cells express several molecules on their surface membranes that are important in regulation of coagulation. Examples are **heparan sulfate** and **thrombomodulin**, which activate anticoagulant systems (antithrombin and the protein C-protein S system, respectively).
- **Endothelial cell metabolic products:** Endothelial cells produce a variety of metabolic products that are critical in the prevention of thrombosis, including *tissue plasminogen activator* (**t-PA**), the primary initiator of the fibrinolytic system; *tissue factor pathway inhibitor* (**TFPI**), which inhibits coagulation via the TF-VIIa-Xa complex; and *prostacyclin* (PGI_2), a potent vasodilator and platelet antagonist. Endothelial cells also produce *nitric oxide* (**NO**; originally called the *endothelial-derived relaxing factor* [EDRF]), which is a potent vasodilator and platelet antagonist, and *endothelin*, which is a potent vasoconstrictor.

DEFECTS IN THE BLOOD VESSEL WALL

- **Hereditary hemorrhagic telangiectasia (HHT;**
- **Scurvy:**
- **Vasculitis:**
- **Amyloidosis:**
- **Corticosteroid excess:**
- **Senile purpura:**

PRIMARY VERSUS SECONDARY HEMOSTASIS

Coagulation (clotting) is traditionally divided into two systems: **primary hemostasis** and **secondary hemostasis**. This division is artificial, but it helps organize our thinking about hemostasis and corresponds to relatively distinct clinical syndromes. *Recognition of bleeding as involving primary or secondary hemostasis is critical in organizing the diagnostic and therapeutic approach to bleeding disorders.*

Primary Hemostasis

Primary hemostasis primarily involves *platelets* and *vWF* and results in the formation of a platelet plug. If the endothelial injury is small, this may be adequate to stop bleeding. However, if the injury is greater, participation by the coagulation cascade is required. The various causes of defects in the primary hemostasis system are listed in Table 20–1.

Secondary Hemostasis

Secondary hemostasis primarily involves the *coagulation cascade proteins*, which ultimately results in the conversion of fibrinogen to fibrin; fibrin polymerizes to form a clot. The fibrin clot is cross-linked and stabilized by factor XIIIa. The various causes of defects in the secondary hemostasis system are listed in Table 20–2.

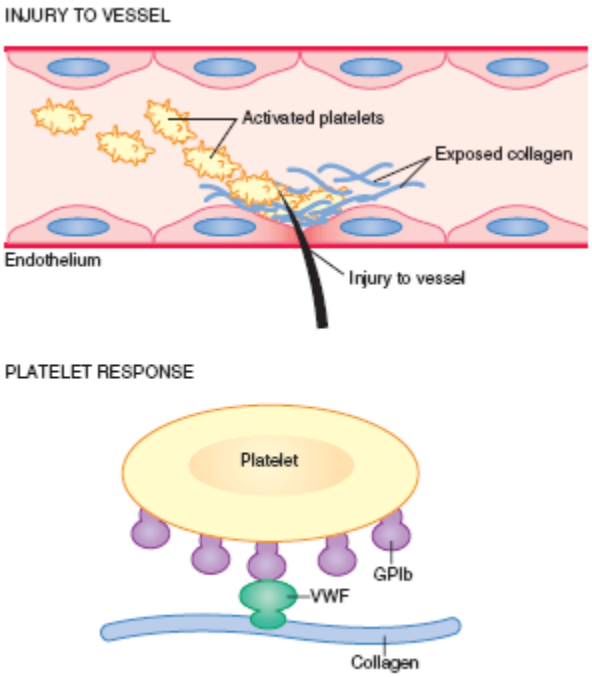


Figure 15.1 Platelet response to vascular injury.

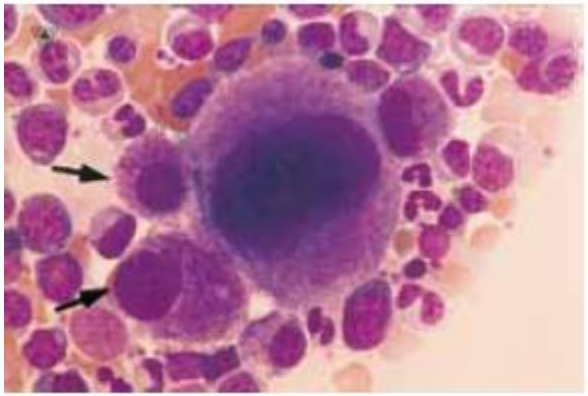


Figure 15.2 Megakaryocyte, the platelet parent cell.

Figure 15.3 Schematic diagram of platelet morphology.

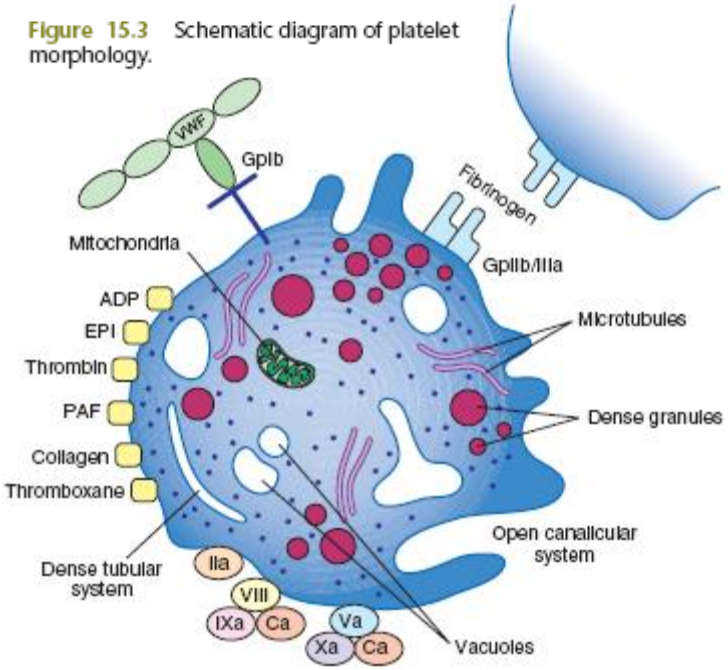


Table 15.1 The Four Functional Platelet Zones

1. The peripheral zone is associated with platelet adhesion and aggregation.
2. The sol gel zone provides a cytoskeletal system for platelets and contact when the platelets are stimulated.
3. The organelle zone contains three types of granules: alpha, dense bodies, and lysosomes.
4. The membrane system contains a dense tubular system in which the enzymatic system for the production of prostaglandin synthesis is found.

There are three groups in which coagulation factors can be classified:

1. The *fibrinogen* group consists of factors I, V, VIII, and XIII. They are consumed during coagulation. Factors V and VIII are labile and will increase during pregnancy and inflammation.
2. The *prothrombin* group: Factors II, VII, IX, and X all are dependent on vitamin K during their synthesis. This group is stable and remains preserved in stored plasma.
3. The *contact* group: Factor XI, factor XII, prekallikrein, and high-molecular-weight kininogen (HMWK) are involved in the intrinsic pathway, moderately stable, and not consumed during coagulation.[5]

The coagulation factors and their actions are listed in (Table 15.2).

Table 15.2 • Factor Facts

Factor	Inheritance	Half-life (hr)	Clinical Picture If Deficient	Factor for Hemostasis	Screening Tests
I	Autosomal dominant	64 to 96	Bleed with trauma, stress, mucosal, umbilical stump, intracranial, gastrointestinal	40 to 50 mg/dL	↑ PT and aPTT
II	Autosomal recessive	48	Severe bleed, mucous membrane, spontaneous	20% to 30%	↑ PT and aPTT
V	Autosomal recessive	12	Moderate-severe bleed, mucosal, large ecchymoses	10% to 15%	↑ PT and aPTT
VII	Autosomal recessive	4 to 6	Intra-articular bleed, severe mucosal, epistaxis, hemarthrosis, genitourinary, gastrointestinal, and intrapulmonary	10% to 15%	↑ PT
VIII	Sex-linked recessive	15 to 20	Severity based on levels, hematuria, hemarthrosis, intra-articular, intracranial	>10%	↑ aPTT
IX	Sex-linked recessive	24	Severe mucous membrane, deep tissue, intra-muscular	>10%	↑ aPTT
X	Autosomal recessive	32	Mucous membrane, skin hemorrhages	10% to 15%	↑ PT and aPTT
XI	Autosomal recessive	60 to 80	Severity of bleeds vary, not proportional to factor level	30%	↑ aPTT
XII	Autosomal recessive and dominant	50 to 70	Hemorrhage is rare, risk for thrombosis	?	↑ aPTT
XIII	Autosomal recessive	40 to 50	Only homozygotes bleed, deep tissue muscle, intracranial bleed	10%	Normal PT and aPTT

Factor I, Fibrinogen

Substrate for thrombin and precursor of fibrin, it is a large globulin protein. Its function is to be converted into an insoluble protein and then back to soluble components. When exposed to thrombin, two peptides split from the fibrinogen molecule, leaving a fibrin monomer to form a **polymerized** clot.

Factor II, Prothrombin

Precursor to thrombin, in the presence of Ca^{2+}, it is converted to thrombin (IIa), which in turn stimulates platelet aggregation and activates cofactors protein C and factor XIII. This is a vitamin K–dependent factor.

Factor III, Thromboplastin

Tissue factor activates factor VII when blood is exposed to tissue fluids.

Factor IV, Ionized Calcium

This active form of calcium is needed for the activation of thromboplastin and for conversion of prothrombin to thrombin.

Factor V, Proaccelerin or Labile Factor

This is consumed during clotting and accelerates the transformation of prothrombin to thrombin. A vitamin K–dependent factor, 20% of factor V is found on platelets.

Factor VI, Nonexistent

Factor VII, Proconvertin or Stable Factor

This is activated by tissue thromboplastin, which in turn activates factor X. It is a vitamin K–dependent factor.

Factor VIII, Antihemophilic

This cofactor is used for the cleavage of factor X-Xa by IXa. Factor VIII is described as VIII/vWF:VIII:C active portion, measured by clotting, VIII:Ag is the antigenic portion, vWF:Ag measures antigen that binds to endothelium for platelet function; it is deficient in hemophilia A.

Factor IX, Plasma Thromboplastin Component

A component of the thromboplastin generating system, it influences amount as opposed to rate. It is deficient in hemophilia B, also known as Christmas disease. It is sex linked and vitamin K–dependent.

Factor X, Stuart-Prower

Final common pathway merges to form conversion of prothrombin to thrombin, activity also related to factors VII and IX. It is vitamin K–dependent and can be independently activated by Russell's viper venom.

Factor XI, Plasma Thromboplastin Antecedent

Essential to intrinsic thromboplastin generating of the cascade, it has increased frequency in the Jewish population. Bleeding tendencies vary, but there is the risk of postoperative hemorrhage.

Factor XII, Hageman factor

This surface contact factor is activated by collagen. Patients do not bleed but have a tendency to thrombosis.

Factor XIII, Fibrin Stabilizing Factor

In the presence of calcium, this transaminase stabilizes polymerized fibrin monomers in the initial clot. This is the only factor that is not found in circulating plasma.

High-Molecular-Weight Kininogen

This surface contact factor is activated by kallikrein.

Prekallikrein, Fletcher Factor

This is a surface contact activator, in which 75% is bound to HMWK.

Table 1.1 Procoagulant clotting factors.

Current nomenclature	*Name*	*Function*
Factor I	Fibrinogen	Precursor of fibrin
Factor II	Prothrombin	Serine protease in prothrombinase complex
(Factor III)	Calcium	Cofactor
(Factor IV)	Tissue factor	Initiation of coagulation
Factor V	Proaccelerin	Cofactor in prothrombinase complex
Factor VII	Proconvertin	Initiation of coagulation
Factor VIII	Antihemophilic factor	Cofactor in tenase complex
Factor IX	Christmas factor	Serine protease in tenase complex
Factor X	Stuart–Prower factor	Serine protease in prothrombinase complex
Factor XI	Plasma thromboplastin antecedent	Amplification of coagulation
Factor XII	Hageman factor	Contact factor
Factor XIII	Fibrin stabilizing factor	Cross-linkage of fibrin
Prekallikrein	Fletcher factor	Contact factor
High molecular weight kininogen	Fitzgerald factor	Contact factor

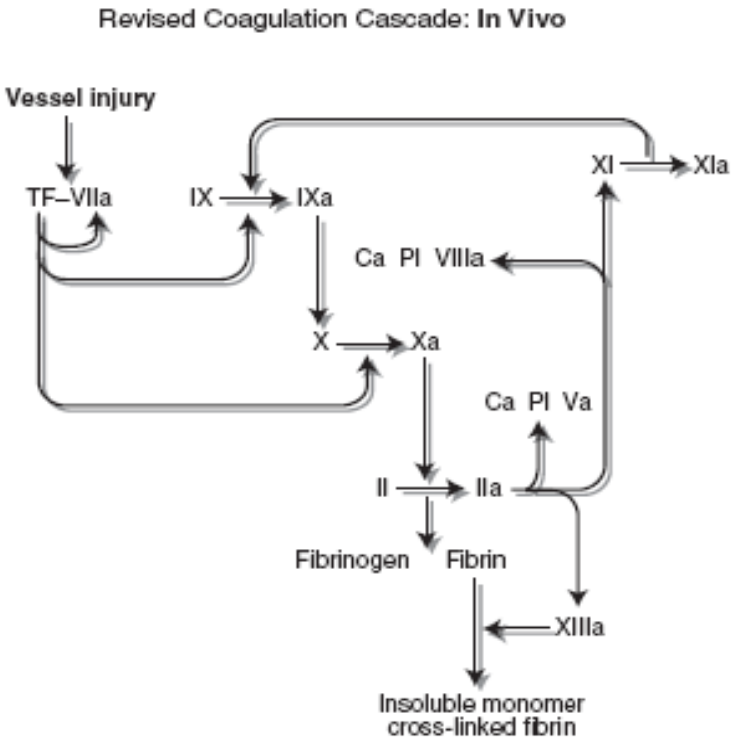


Figure 15.5 In vivo coagulation cascade.

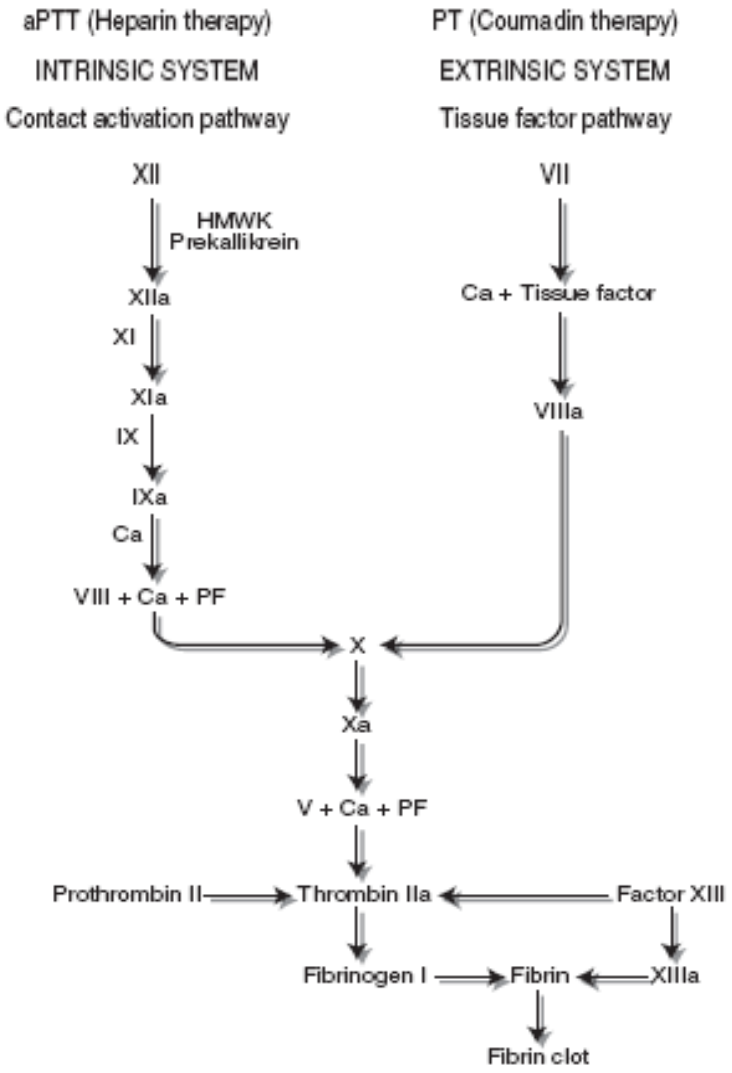


Figure 15.6 In vitro coagulation cascade.

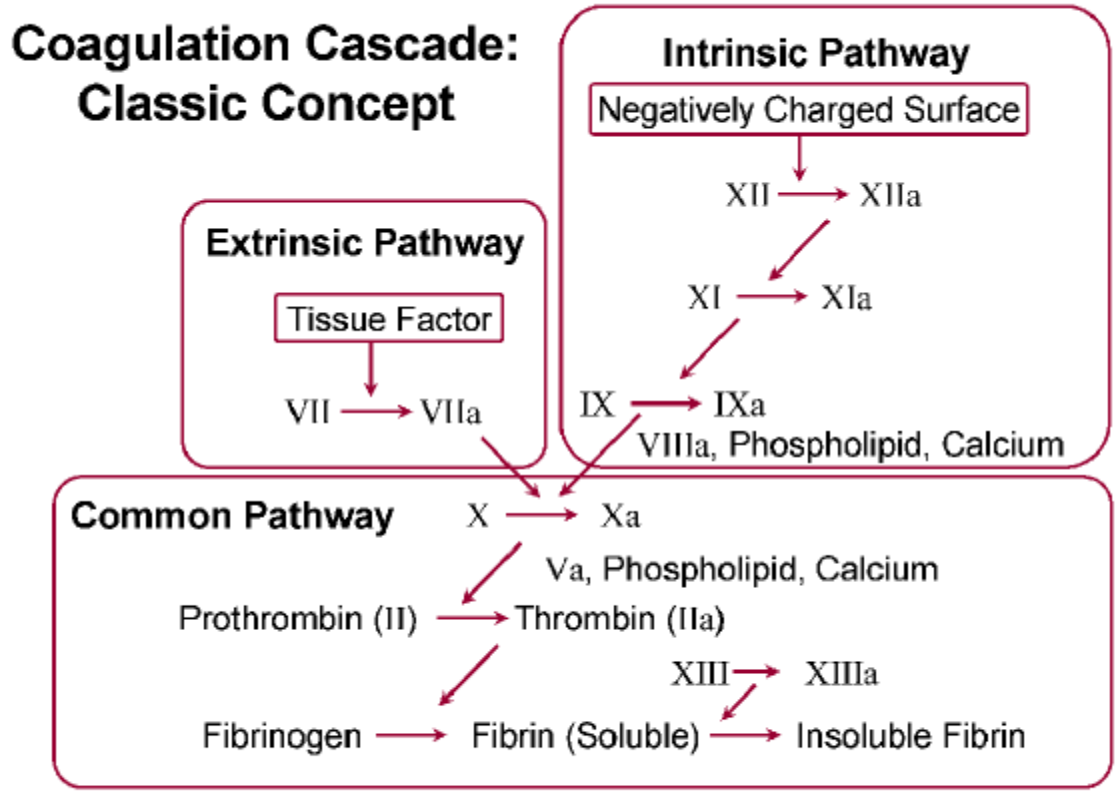


Figure 20–1 Classic concept of the coagulation cascade.

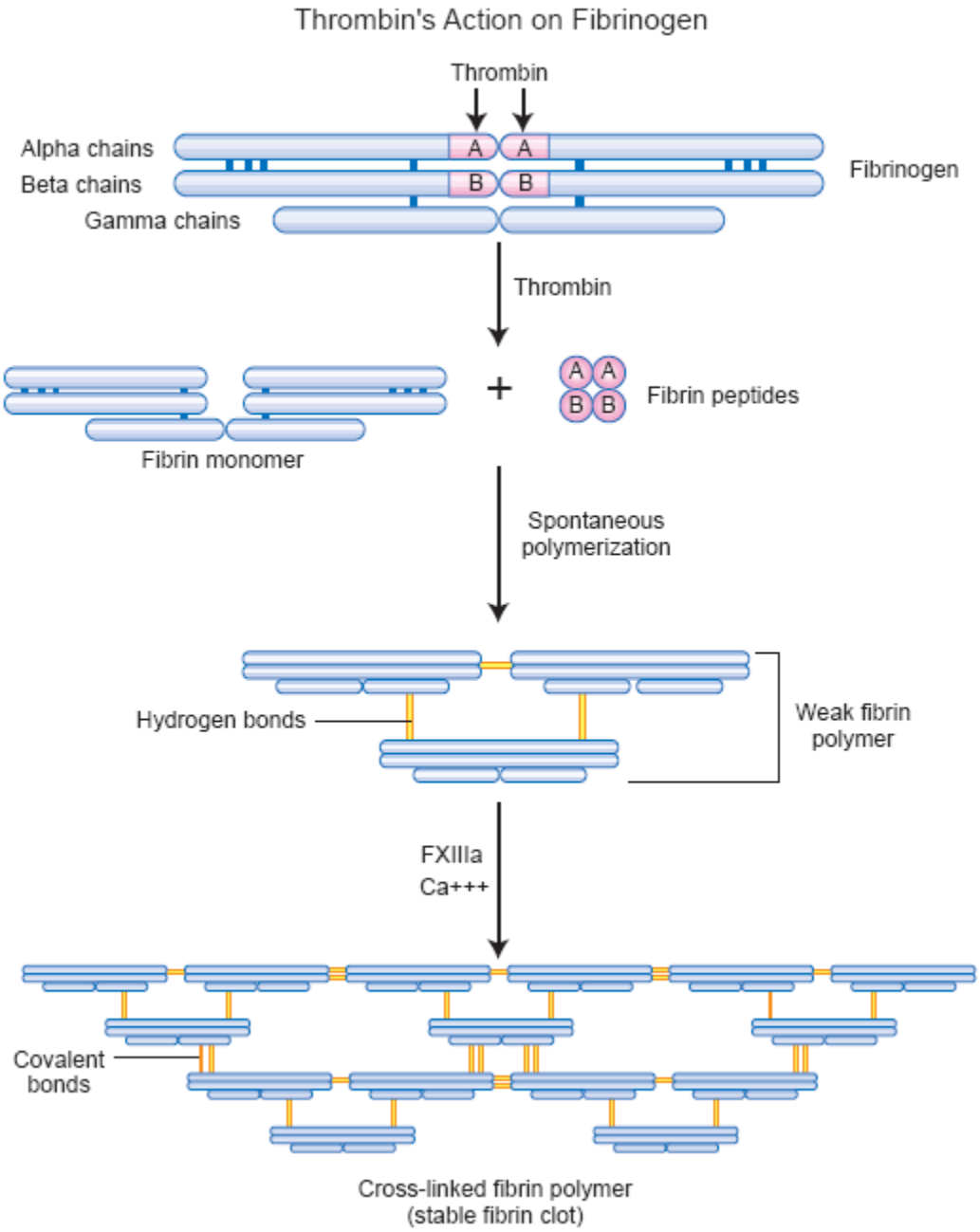


Figure 18.1 Thrombin's activity on fibrinogen, from fibrin monomer to fibrin polymer.

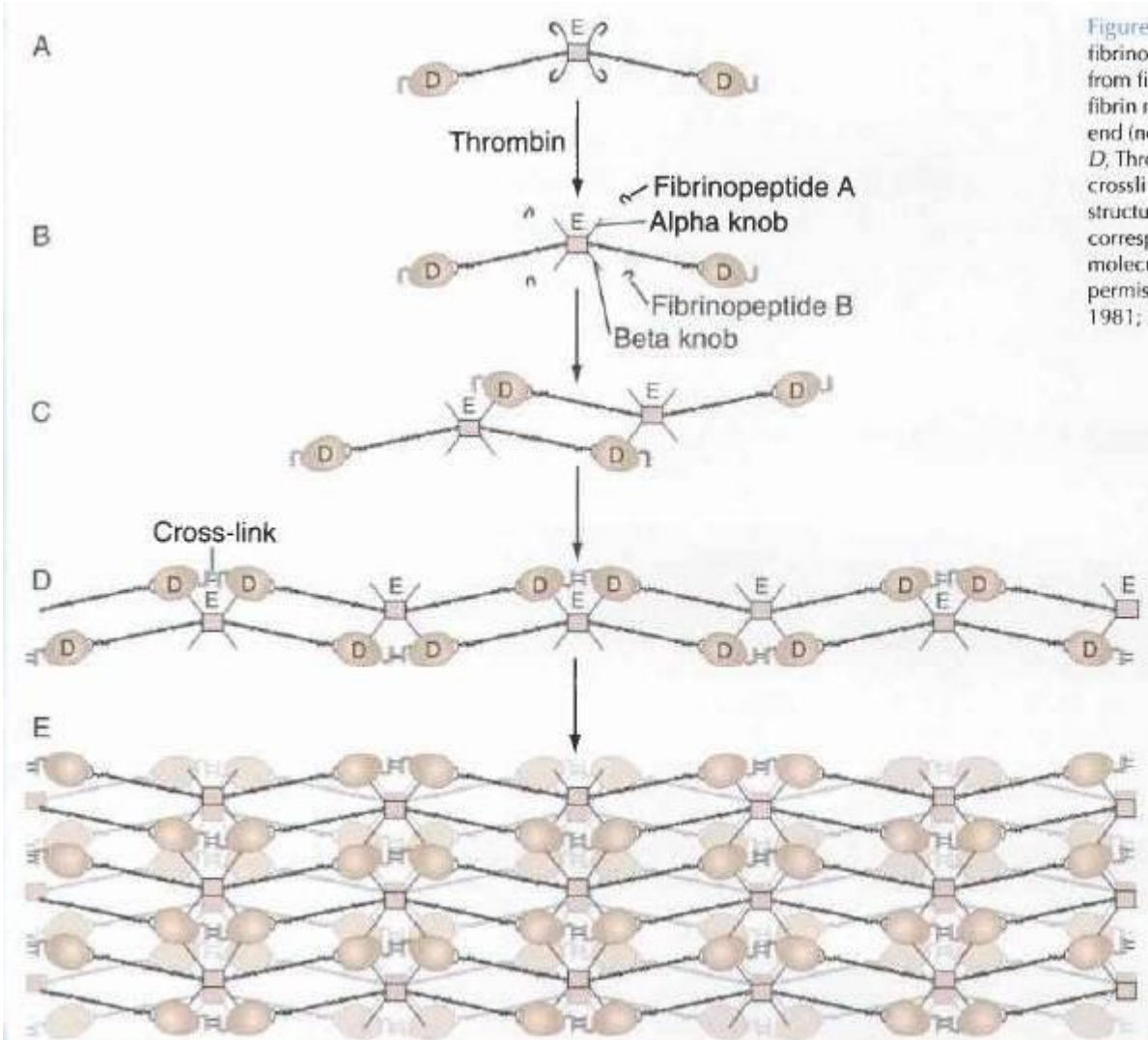


Figure 38–3 Formation of a fibrin clot. *A*, Schematic of fibrinogen. *B*, Thrombin proteolyzes fibrinopeptides A and B from fibrinogen to leave soluble fibrin monomer. Soluble fibrin monomer then associates side-to-side (*C*) and end-to-end (not shown, for clarity) to form fibrin polymers. *D*, Thrombin-activated factor XIII (factor XIIIa) covalently crosslinks the fibrin polymers into an increasingly complex structure and ultimately insoluble clot (*E*). Note that 'E' corresponds to the central domain of the original fibrinogen molecule, and 'D' to the peripheral domains. (Modified with permission from Doolittle RF: Fibrinogen and fibrin. Sci Am 1981; 245:126–135.)

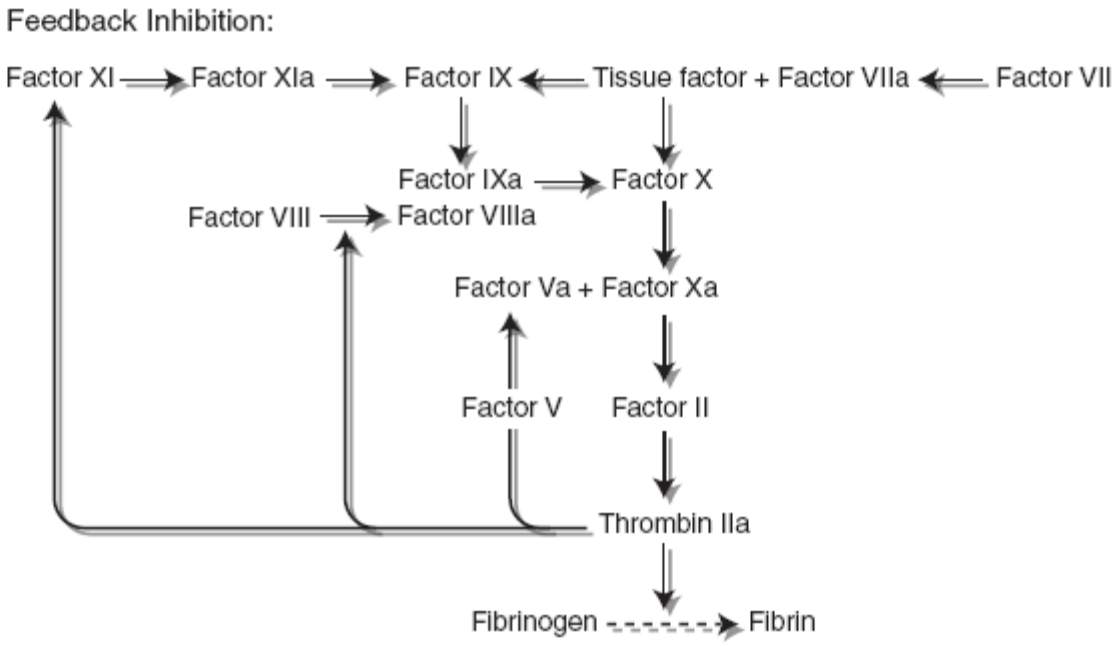


Figure 15.7 Feedback inhibition. Note the role of thrombin in the activation and deactivation of coagulation factors.

Coagulation Inhibitors

Inhibitors are soluble plasma proteins that are natural anticoagulants. They prevent the initiation of the clotting cascade. There are two major inhibitors in plasma that keep the activation of coagulation under control. These inhibitors are:

1. Protease inhibitors: inhibitors of coagulation factors, which include
   - Antithrombin
   - Heparin cofactor II
   - Tissue factor pathway inhibitor
   - Alpha-2-antiplasmin
   - C1
2. The protein C pathway: inactivation of activated cofactors, which includes
   - Protein C and protein S

Table 15.3 Serine Protease Inhibitors

Inhibitor	Specificity
Antithrombin (AT)	IIa, Xa, IXa
Alpha-2-macroglobulin	Nonspecific
Tissue factor pathway inhibitor	Xa, VIIa/TF complex
Heparin cofactor II	IIa
Alpha-2 protease inhibitor	XIa, elastase
CI inhibitor	XIIa, kallikrein, XIa, CI (complement system)

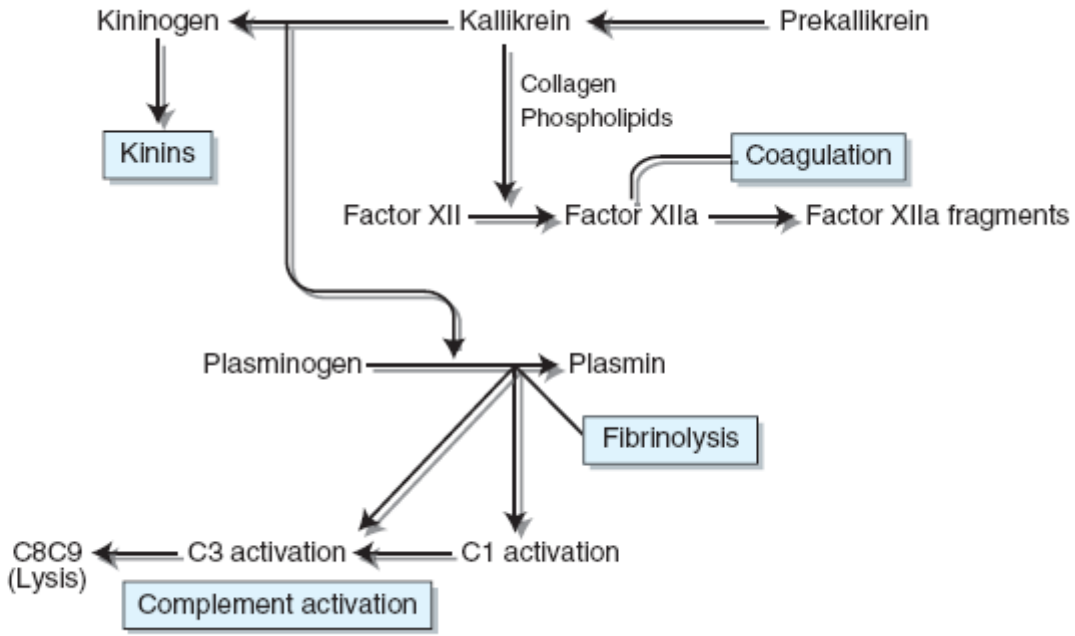


Figure 15.8 Interrelationships between the coagulation, fibrinolytic, complement, and kinin systems.

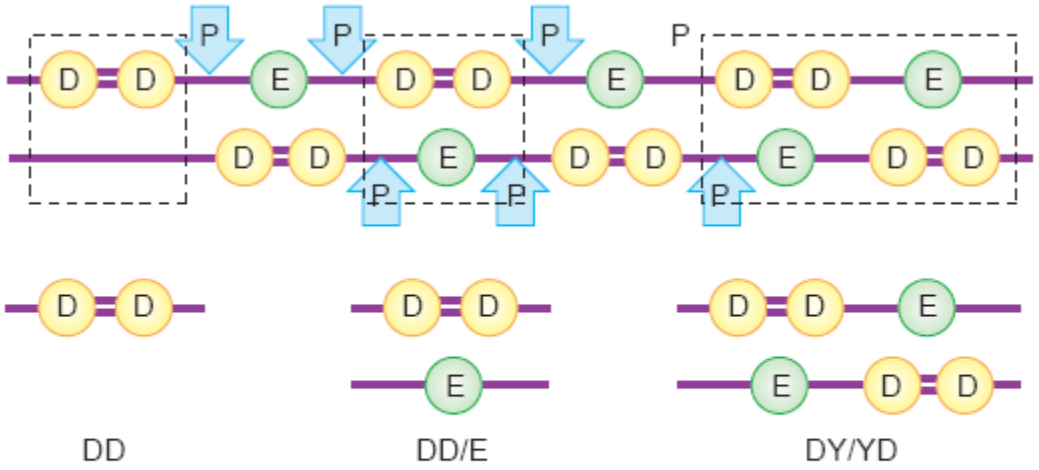
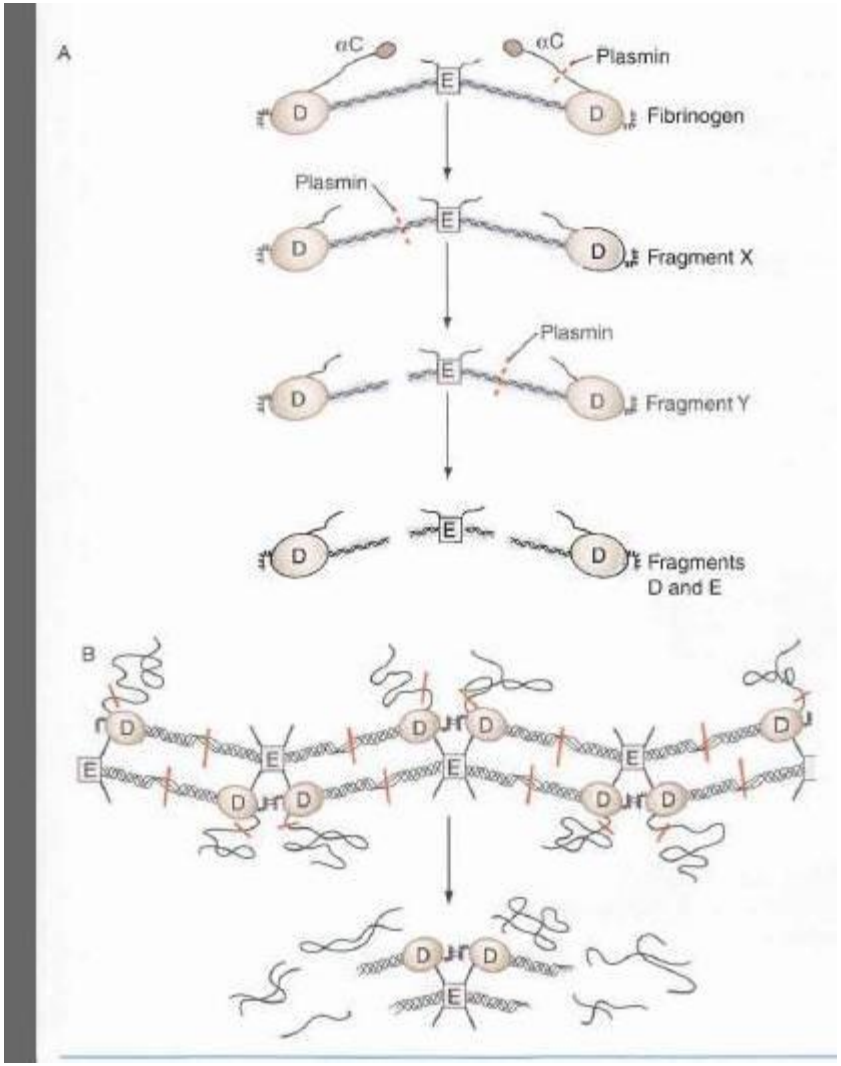


Figure 18.3 The formation of D-dimer and fibrin degradation products. P, plasmin; D, D domain; E, E domain.

P= Plasmin
D= D domain
E= E domain


A
αC
αC
Plasmin
E
D
D
Fibrinogen
Plasmin
E
D
D
Fragment X
Plasmin
E
D
D
Fragment Y
E
D
D
Fragments
D and E
B
D
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Causes of Primary Hemostasis Deficiencies

Thrombocytopenia

Inherited disorders of platelet function: Bernard-Soulier syndrome, Glanzmann's thrombasthenia, storage pool deficiency

von Willebrand's disease

Medications: aspirin, ticlopidine, clopidogrel, antibiotics (penicillins, cephalosporins), antihistamines, cough medications (guaifenesin), and many others

Acquired disorders of platelet function: myelodysplasia, increased fibrin degradation products

Causes of Secondary Hemostasis Disorders

Hemophilias: inherited decrease in clotting factor levels or production of abnormal clotting factors

Decreased fibrinogen

Liver disease

Warfarin drugs: interfere with synthesis of vitamin K–dependent clotting factors

Fibrin degradation products (also interfere with platelet function)

Table 38–2 Patterns of Clinical Bleeding in Disorders of Hemostasis

Characteristics	Primary Hemostasis (Platelet/Vascular Problem)	Secondary Hemostasis (Coagulation Factor Problem)
Onset	Spontaneous, immediate after trauma	Delayed after trauma
Sites	Skin, mucous membranes	Deep tissues
Form	Petechiae, ecchymosis	Hematomas
Mucous membrane	Common (nasal, oral, gastrointestinal, genitourinary)	Less common
Other sites	Rare	Joint, muscle, central nervous system, retroperitoneal
Clinical examples	*Thrombocytopenia*, platelet defects, von Willebrand disease, scurvy	Factor deficiency, liver disease, acquired inhibitors

Table 11–1

Causes of Thrombocytosis

Artifact (pseudothrombocytosis):

- Schistocytes
- Acute leukemia (white cell fragments)
- Cryoglobulinemia
- Microorganisms

Primary (essential) thrombocythemia; other chronic myeloproliferative disorders

Secondary (reactive) thrombocytosis:

- Acute stress or physical exertion
- Inflammation: rheumatoid arthritis, other autoimmune disorders, inflammatory bowel disease
- Infections
- Malignancies
- Acute hemorrhage
- Acute hemolysis
- Iron deficiency
- Surgery
- Post-splenectomy
- Rebound thrombocytosis following thrombocytopenia

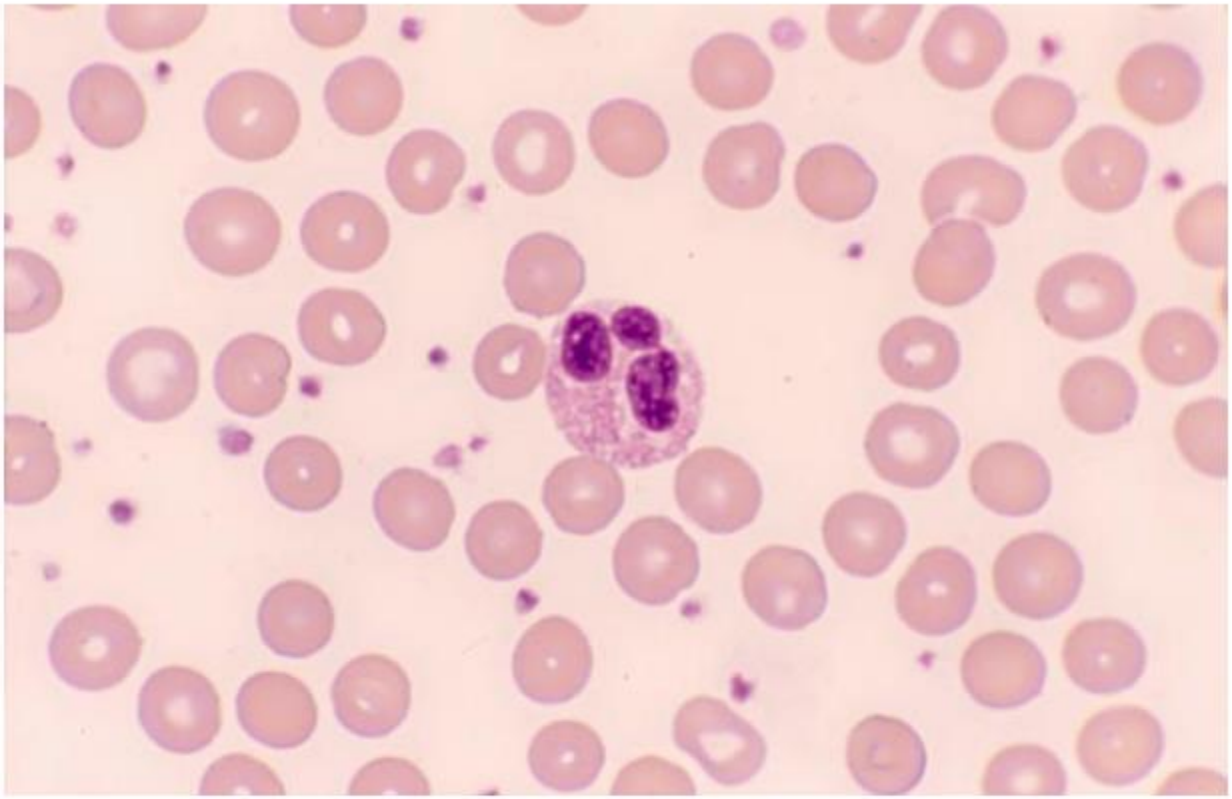


Figure 11–1 Thrombocytosis (post-splenectomy). Platelet count of 700,000/μL after splenectomy.

Table 11–2

Distinction of Reactive Thrombocytosis from Primary Thrombocythemia

Characteristic	Reactive Thrombocytosis	Essential Thrombocythemia
Known cause of reactive thrombocytosis	Present	Absent
Platelet count	Typically 500,000–700,000/μL; *usually* <1,000,000/μL	Almost always >600,000/μL; often >1,000,000/μL
Thrombosis or hemorrhage	No	Often
Splenomegaly	No	Yes
Giant platelets and megakaryocyte fragments in blood	No	Yes
Bone marrow fibrosis	No	Yes
Megakaryocyte clusters on bone marrow biopsy	No	Yes
Abnormal cytogenetic analysis on bone marrow	No	Occasional

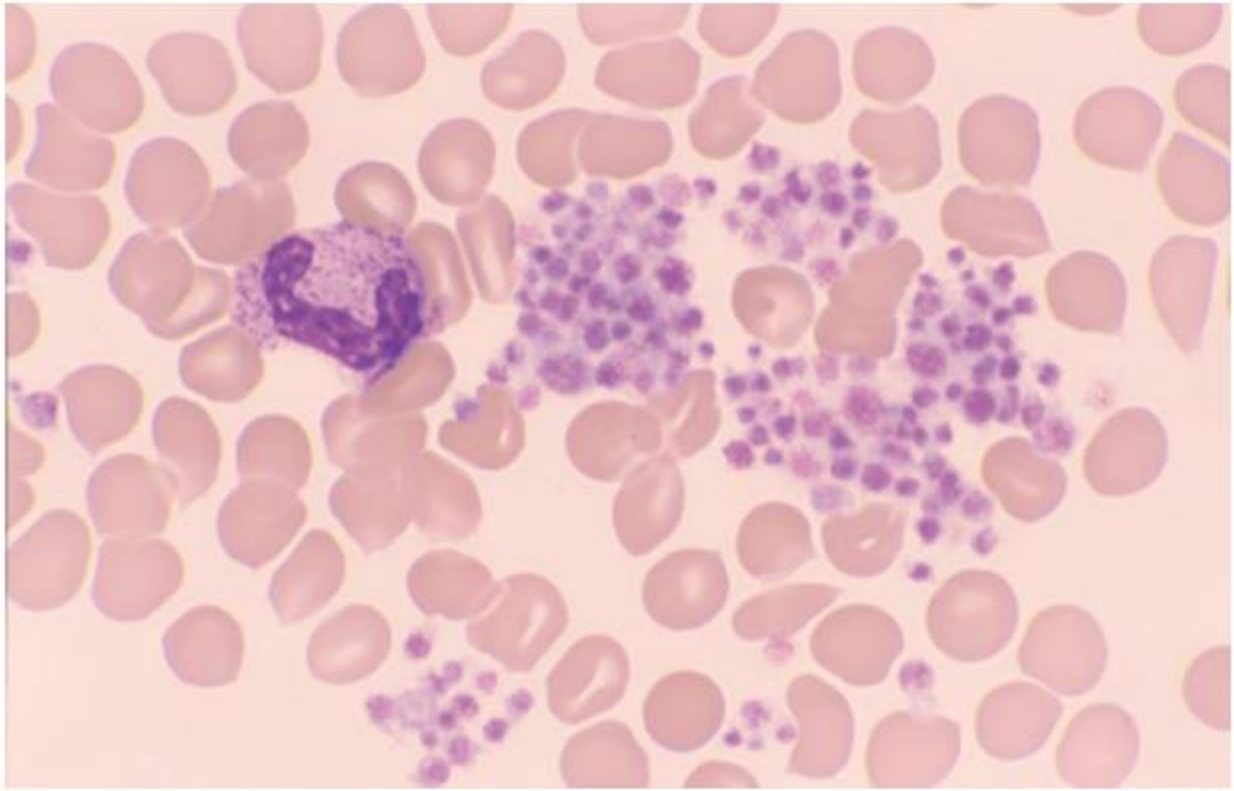


Figure 11–2 Platelet clumping (pseudothrombocytopenia). Large platelet clumps on the blood smear from a 21-year-old asymptomatic woman. The hematology analyzer reported a platelet count <11,000/μL. Specimen anticoagulated with citrate showed a normal platelet count.

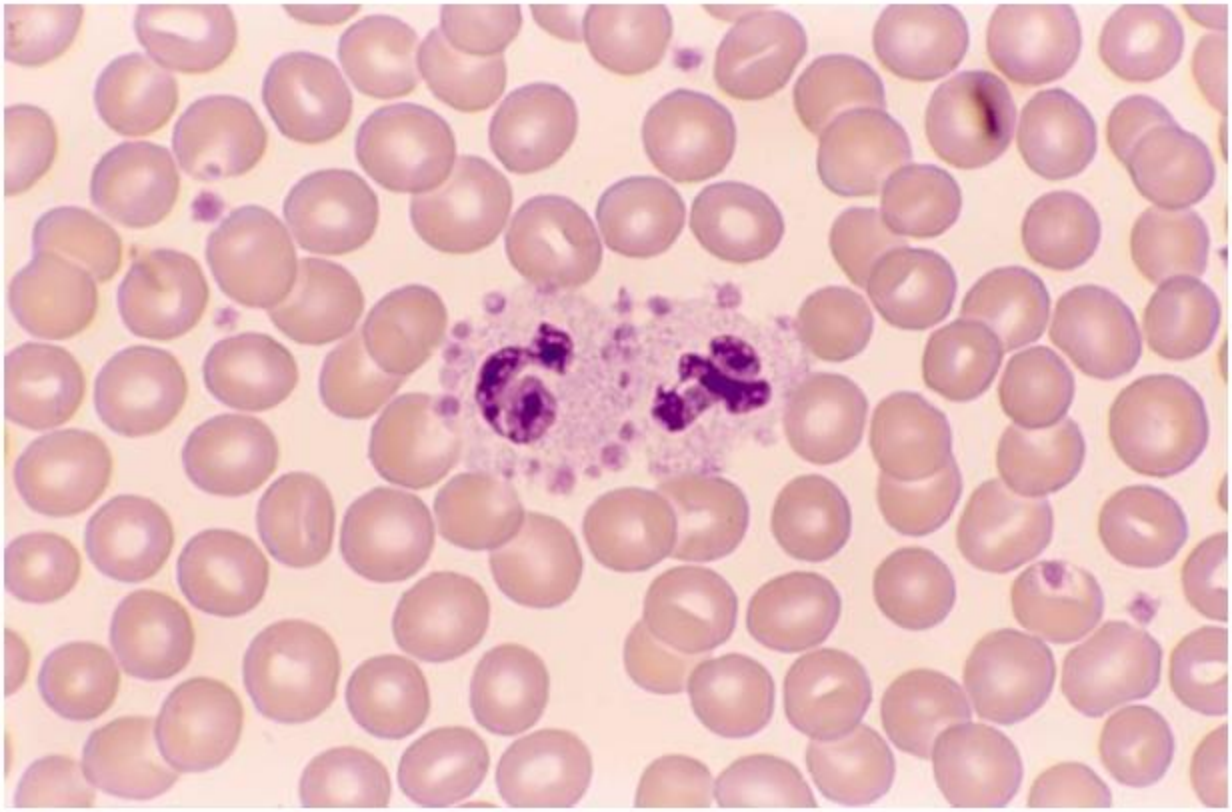


Figure 11–3 Platelet satellitism. Platelets adhering to the surface of a neutrophil. In this case, the reported platelet count was only slightly decreased.

Table 11–4

Causes of Thrombocytopenia

Pseudothrombocytopenia (artifactual)
- Platelet clumping
- Platelet satellitism

Inherited
- Thrombocytopenia–absent radii (TAR) syndrome
- Wiskott-Aldrich syndrome
- May-Hegglin anomaly
- Bernard-Soulier syndrome
- Gray platelet syndrome

Congenital non-inherited
- Intrauterine viral infection
- Maternal drugs or medications: thiazide diuretics, oral hypoglycemic agents, ethanol, steroids, quinine, and quinidine
- Maternal ITP or other immunologic diseases
- Neonatal alloimmune thrombocytopenia

Acquired

Immune:
- Idiopathic
- Infections: viruses (EBV, CMV, HIV), bacteria, riskettsiae, *Mycoplasma*, others
- Drugs: quinidine, quinine, gold, rifampin, trimethoprim-sulfamethoxazole, others
- Lymphoproliferative disorders
- Autoimmune (collagen vascular) diseases
- Post-transfusion purpura
- Other

Non-immune:
- Infections
- Disseminated intravascular coagulation (DIC)
- Thrombotic thrombocytopenic purpura (TTP)
- Hemolytic-uremic syndrome (HUS)
- Preeclampsia/eclampsia and the HELLP syndrome
- Massive transfusion
- Gestational thrombocytopenia

Platelet sequestration in the spleen
- Hypersplenism: usually associated with anemia and/or leukopenia

INHERITED DISORDERS OF COAGULATION

There are a large number of inherited disorders of coagulation; however, only three are relatively common: **vWD**, **factor VIII deficiency** (**hemophilia A**), and **factor IX deficiency** (**hemophilia B**; **Christmas disease**). All of the others are rare. *It is critical to know the clinical manifestations, inheritance patterns, diagnostic tests, and treatment of these three diseases.*

von Willebrand's Disease

von Willebrand disease is the most common inherited disorder of primary hemostasis. The prevalence of vWD mutations may be as high as 1 to 2% of the population, although many are never diagnosed; the prevalence of *clinically evident* vWD is much lower. *The clinical and laboratory manifestations of vWD are extremely heterogeneous, and diagnosis can sometimes be difficult.*

Three main subtypes of vWD have been defined:

Table 39–8 Classification of von Willebrand Disease

Type	Description
1	Partial quantitative deficiency of von Willebrand factor (vWF)
2	Qualitative deficiency of vWF
2A	Decreased platelet-dependent vWF function with selective deficiency of high-molecular-weight multimers
2B	Increased affinity for platelet glycoprotein Ib
2M	Decreased platelet-dependent vWF function with high-molecular-weight multimers present
2N	Markedly decreased binding of factor VIII to vWF
3	Complete deficiency of vWF

Table 16.3 Basic Test Profile for vWD

- Platelet count—measured by automated methods
- PTT—measures anticoagulant portion of the factor VIII molecule
- Bleeding time—measures adhesion of platelets to site of injury
- vWF activity—measured by ristocetin-induced platelet aggregation (RIPA)
- vWF antigen—measured by immunoassay

Most patients will have variable test results. It is recommended that this test profile be performed multiple times within a time period to aid in diagnosis.

Table 16.4 Primary von Willebrand's Disease Derivatives*

	Type 1	Type 2	Type 3
Frequency	70% to 80%	15% to 20%	Rare
Genetics	Autosomal dominant	Autosomal dominant	Autosomal recessive
Bleeding time	↑ or N	↑	↑
PTT	↑ or N	↑ or N	↑
RIPA	↑ or N	↑	↑
vWF agn.	↓	↓	Absent

*Secondary vWD variants include types 2A, 2B, 2M, and 2N: these are not discussed.

The Hemophilias

The hemophilias are *inherited disorders of the coagulation cascade.* Deficiency of **factor VIII** (**hemophilia A**) is by far the most common (~85% of cases). **Factor IX** deficiency (**hemophilia B**) is second (~15%), and all others are rare. The incidence of hemophilia A is estimated at 1 per 5,000 to 10,000 male births in the United States; the incidence of hemophilia B is approximately 1 in 30,000 male births. **Hemophilia A and B** are both inherited as **X-linked recessive**: women are carriers, men develop the disease. All of the other factor deficiencies are inherited as autosomal recessive. **Factor XI** deficiency (sometimes called **hemophilia C**) is the third most common inherited disorder of coagulation factors but is much less common than deficiency of factors VIII or IX. In the United States, factor XI deficiency is most often seen in Ashkenazi Jews (origin from Eastern Europe).

هموفیلی یک اختلال خونریزی دهنده ی ارثی است که فرد مبتلا به آن به علت سطح پایین یا عدم وجود فاکتورهای انعقادی قادر به متوقف کردن روند خونریزی نمی باشد.

Table 20–4

Hemophilia: Factor Level versus Severity*

Severity	Factor Level	Manifestations
Severe:	<1%	Spontaneous bleeding; bleeding with minor surgery or trauma
Moderate:	1–5%	Spontaneous bleeding uncommon; may bleed with surgery or trauma
Mild:	5–20%	No spontaneous bleeding; may bleed with major trauma or surgery

*Generally applies to both factor VIII and factor IX deficiencies; may not apply to deficiency of other factors.

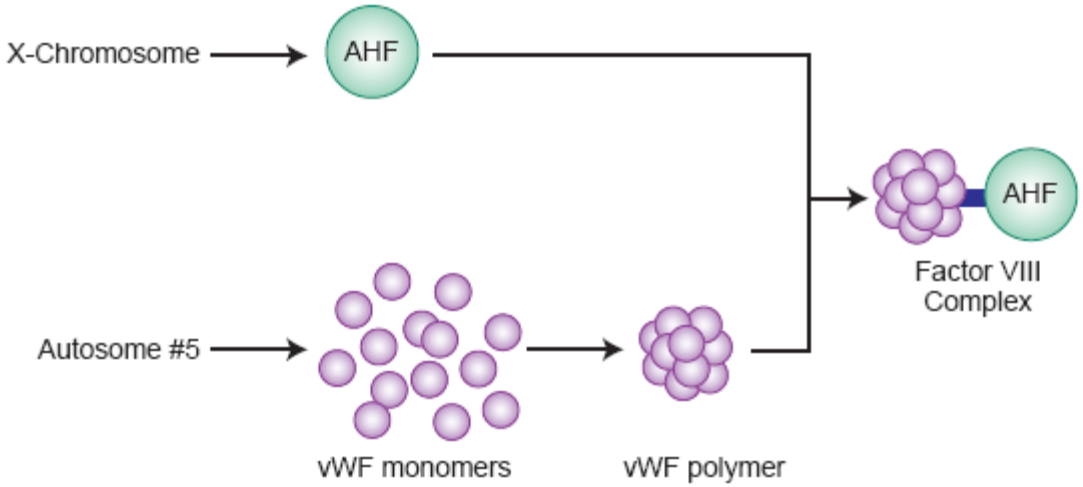


Figure 17.2 Factor VIII complex is controlled by the X chromosome and an autosomal chromosome. This complex transports factor VIII into the circulation. vWF, von Willebrand factor; AHF, antihemophilic factor.

Other Clotting Factor Deficiencies

Deficiencies of other clotting factors occur and can be associated with significant bleeding, but they are rare. The clinical severity of bleeding is not always easy to predict from the type of deficient factor and the level of factor present. For example, it would *seem* that a deficiency in factor V should result in a severe bleeding tendency, similar to that seen with deficiencies in factors VIII or IX. In fact, factor V deficiency usually results in only a mild or moderate bleeding disorder.

ACQUIRED BLEEDING DISORDERS

Acquired bleeding disorders are more common than inherited disorders. Acquired disorders can be of the primary hemostatic system or the secondary hemostatic system, or involve both systems. Unlike the inherited disorders of coagulation, which typically involve an abnormality in one factor or system, acquired bleeding disorders are often complex and involve multiple factors or systems.

Acquired Disorders of Primary Hemostasis

Antiplatelet Drugs
Uremia

Acquired Disorders of Secondary Hemostasis

Liver Disease
Disseminated Intravascular Coagulation

Table 20–7

Causes of Disseminated Intravascular Coagulation (DIC)

Acute DIC
Bacteremia: gram-negative and gram-positive bacteria
Sepsis with other organisms: fungi, mycobacteria, rickettsias, some viruses
Obstetric accidents: retained products of conception, placental abruption, amnionic fluid embolism
Severe trauma, especially head trauma
Burns
Shock or acidosis of any cause
Surgery
Acute hemolytic transfusion reaction
Malignancies: acute leukemia (especially acute promyelocytic leukemia); some carcinomas (especially mucin-producing carcinomas like gastric, prostatic, pancreatic)
Chronic DIC
Malignancies: carcinomas, particularly gastric and pancreatic

HYPERCOAGULABLE STATES (THROMBOPHILIA)

Thrombophilia is the technical term for hypercoagulable states. Virchow originally defined the conditions that predispose to thrombosis as (1) **abnormalities in the blood vessel wall**, (2) **abnormalities in the blood**, and (3) **abnormalities of blood flow** (stasis). His definition remains valid today.

Thrombophilia can be either *inherited* or *acquired*. Suggestions of an inherited thrombophilia include **thrombosis without any predisposing condition** (ie, no surgery, injury, prolonged inactivity), **thrombosis at a young age** (less than about 40 to 45), **thrombosis in unusual sites** (upper extremities, mesenteric vessels, hepatic or portal veins, cerebral veins), and a **family history of thrombosis**. We now know that many individuals with thromboemboli who appear to have an obvious predisposing factor for thrombosis (ie, recent surgery) also have an inherited thrombophilia.

Inherited Hypercoagulable States

Acquired Hypercoagulable States

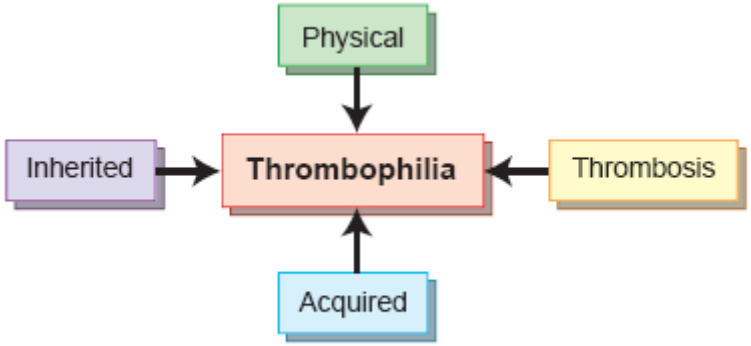


Figure 19.1 Risk factors for thrombosis.

Table 19.2 Conditions Associated With Inherited Thrombosis

- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency
- Prothrombin G20210A
- APCR
- Hyperhomocysteinemia
- Elevated factor VIII
- Factor XII deficiency

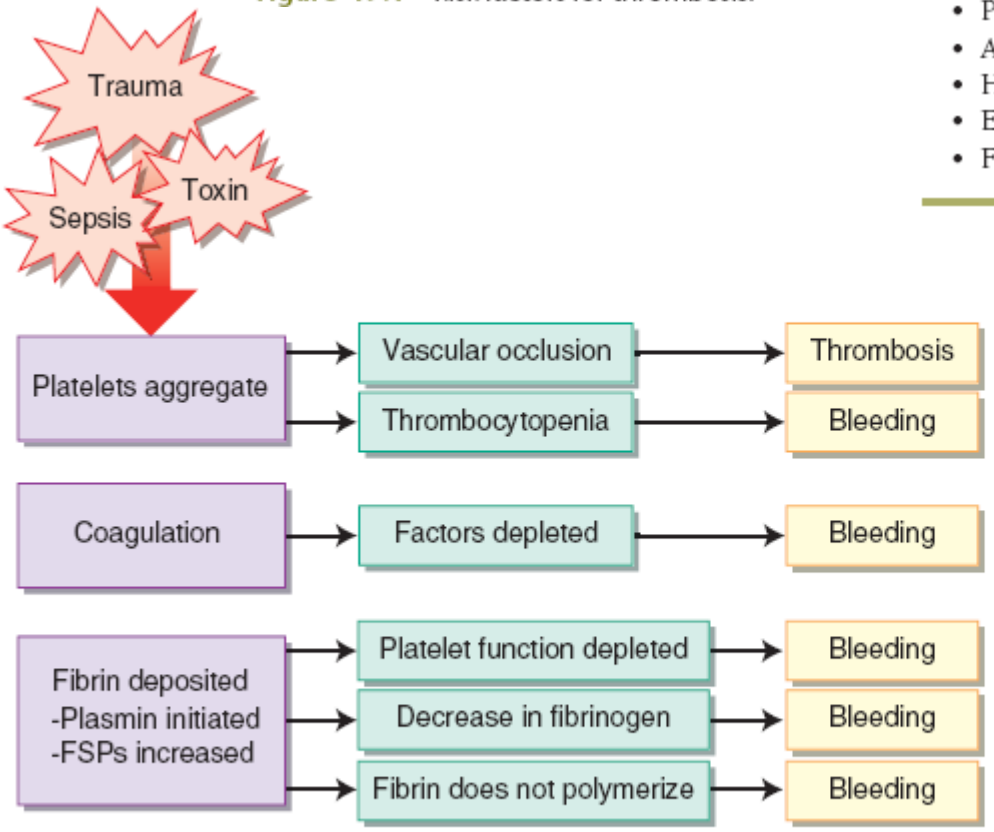


Figure 18.4 Conditions that may precipitate disseminated intravascular coagulation (DIC). Note the multiple pathways. FSPs, fibrin split products.

DVT

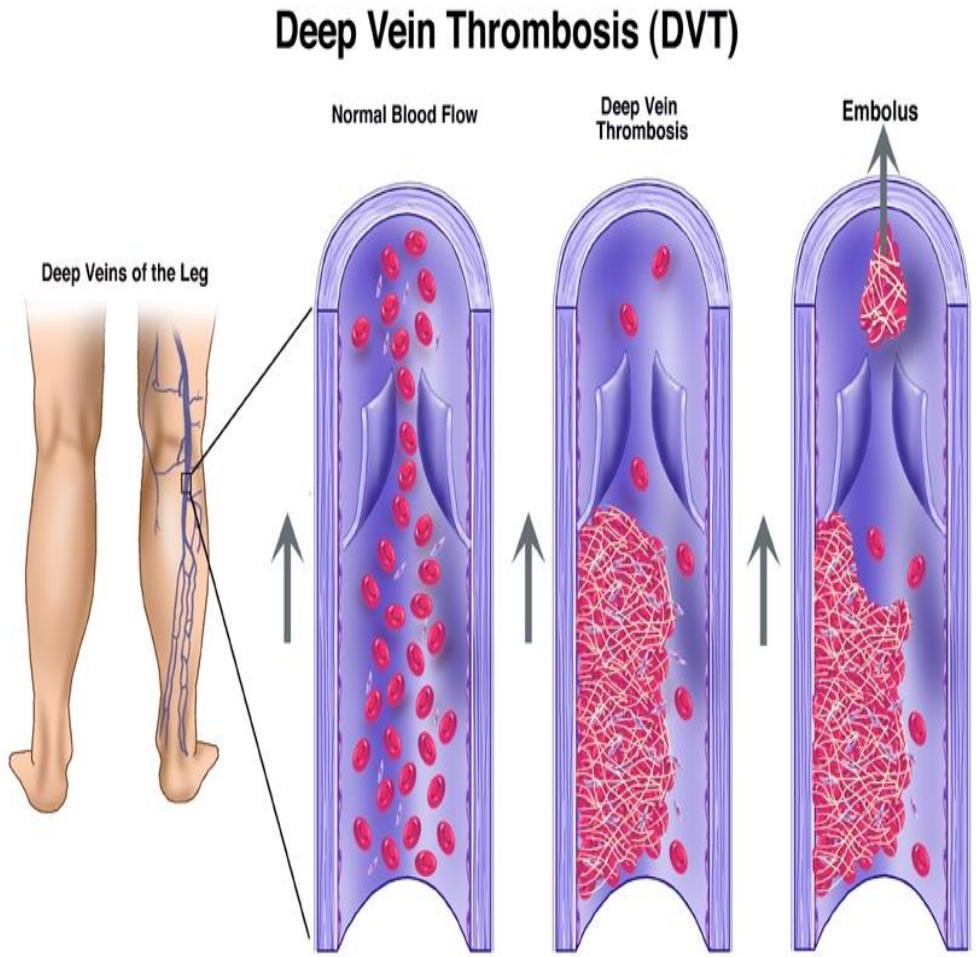

Deep Vein Thrombosis (DVT)
Normal Blood Flow
Deep Vein Thrombosis
Embolus
Deep Veins of the Leg

Table 19.1 Conditions Associated With Acquired Thrombosis

- Cancer
- Surgery (especially orthopedic surgery)
- Liver disease
- Immobility
- Nephritic syndrome
- DIC
- Pregnancy
- Antiphospholipid antibodies
- Drugs
- Others

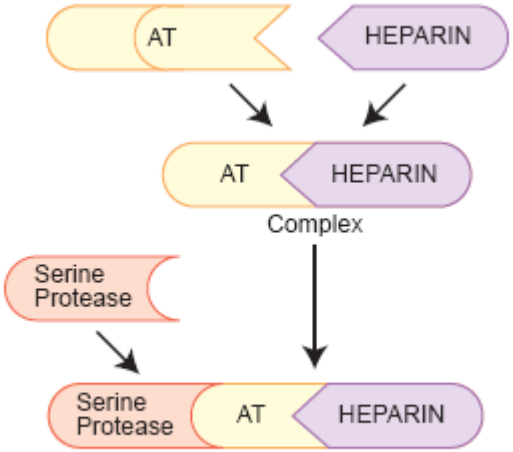


Figure 19.2 Effect of antithrombin on serine proteases.

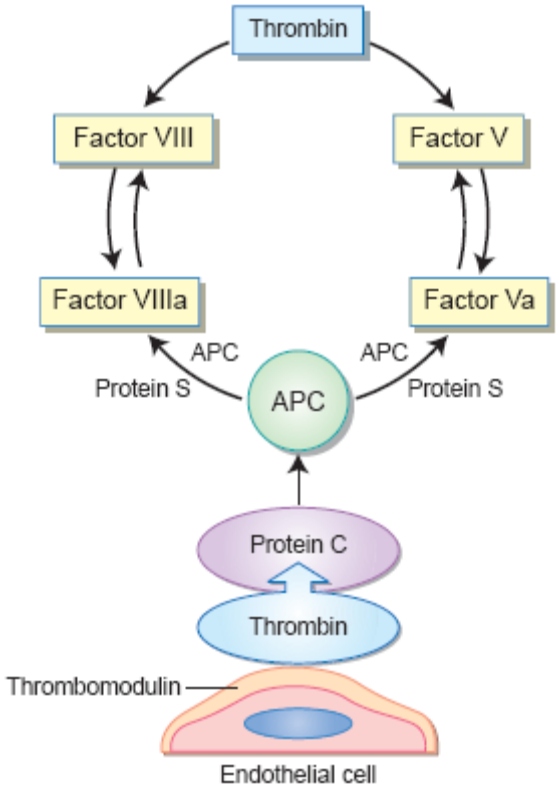


Figure 19.3 Protein C pathway.

Table 19.3 Criteria for the Diagnosis of Lupus Anticoagulant

- Prolongation of at least one phospholipid-dependent tests
- Lack of correction of mixing studies
- Correction of the abnormal result with the addition of excess phospholipids
- Lack of any other specific inhibitor

Table 19.4 Conditions That Require Evaluation for Hypercoagulable States

- Recurrent thrombosis in patients <45 years old
- Patients with a positive family history
- Recurrent spontaneous thromboses
- Thrombosis in unusual sites
- Heparin resistance
- Proteins C and S deficiency
- Thrombosis associated with pregnancy and estrogen therapy
- Unexplained recurrent pregnancy loss

Table 19.5 Screening Laboratory Tests for Hypercoagulable State

- Activated protein C resistance
- Functional assays for antithrombin, protein C, and protein S
- Prothrombin G20210A by polymerase chain reaction
- APTT, DRVVT, mixing studies, and confirmatory test for lupus anticoagulant
- Enzyme-linked immunosorbent assays for anticardiolipin antibody
- Factor VIII activity

APPROACH TO THE PATIENT WITH POSSIBLE DISORDERS OF HEMOSTASIS

It is impossible to describe a single approach that is appropriate for *all* patients who may have a possible disorder of hemostasis. What follows is a general approach, which should get you started in most cases (Table 20–13). The results of history, physical examination, and initial tests will allow you to alter the approach for each specific patient.

- **Always remember that a good history is the most specific and most sensitive diagnostic test for a patient with a possible hemostatic disorder. Doing laboratory tests does NOT substitute for a good history and physical.**

Table 20–13

Approach to the Patient with Possible Disorders of Hemostasis

History

Physical examination

Basic laboratory tests
- PT, PTT
- Fibrinogen level
- CBC with platelet count
- Examination of blood smear

Additional laboratory tests*
- Bleeding time
- Mixing study for prolonged PT or PTT
- Fibrinogen degradation products or D-dimer

Possible hemophilia: factor assays, beginning with factors VIII and IX

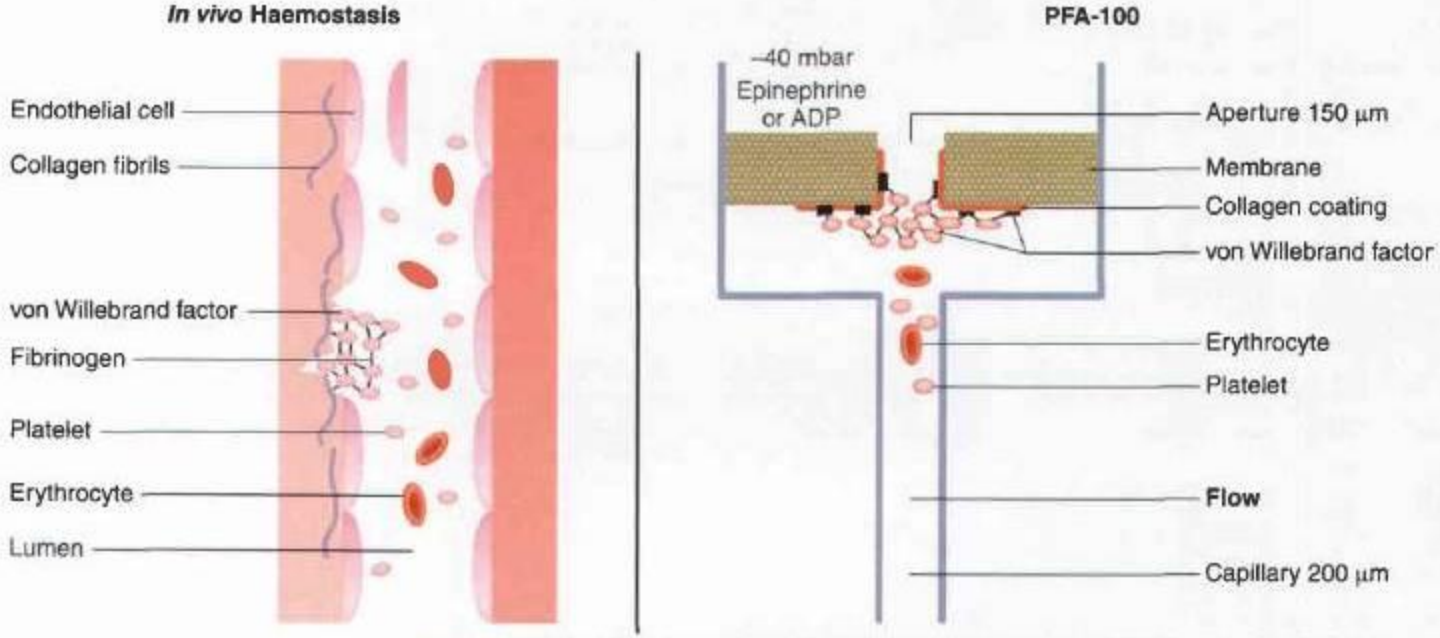
Possible von Willebrand's disease: quantitative assay of vWF, ristocetin co-factor activity, ristocetin-induced platelet aggregation, vWF multimer analysis

*Additional tests performed selectively, based on results of history, physical examination, and initial laboratory tests.

Table 2.2 Interpretation of abnormalities of coagulation screening tests.

Prothrombin time	*APTT*	*Thrombin time*	*Fibrinogen*	*Possible conditions*
Prolonged	Normal	Normal	Normal	Factor VII deficiency
Normal	Prolonged	Normal	Normal	Deficiency of FVIII, FIX, FXI, FXII or contact factor
				Lupus anticoagulant
Prolonged	Prolonged	Normal	Normal	Deficiency of FII, FV or FX
				Oral anticoagulant therapy
				Vitamin K deficiency
				Combined deficiency of FV + FVIII
				Combined deficiency of FII, FVII, FIX, FX
				Liver disease
Prolonged	Prolonged	Prolonged	Normal or low	Hypo- or dysfibrinogenemia
				Liver disease
				Massive transfusion
				DIC

APTT, activated partial prothrombin time; DIC, disseminated intravascular coagulopathy.



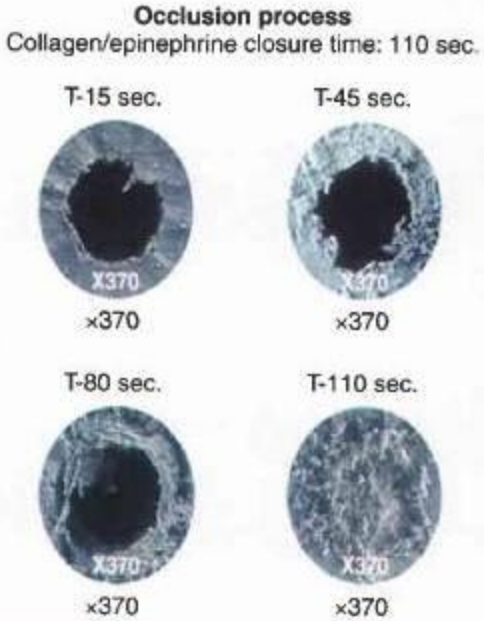


Figure 39–7 PFA-100. *A* (upper right), Diagrammatic representation of PFA-100 flow chamber. Following piercing of a membrane coated with collagen and either epinephrine or ADP, anticoagulated whole blood is exposed both to chemical stimuli and to the biophysical shear resulting from the forced flow through the narrow tubing used in the apparatus. While this in vitro environment shares some similar elements with in vivo hemostasis (shown diagrammatically at the left), it is important to remember that these environments are intrinsically quite different, and the PFA-100 may not always produce results identical to those observed in the far more complex *in vivo* environment. *B* (lower left), Illustration of progressive occlusion of the pierced aperture by platelet thrombi in a collagen/epinephrine membrane in the PFA-100 device. (Images provided by Dade Corporation.)

Table 34.1 Laboratory features of major inherited coagulation disorders.

Condition	PT	APTT	Bleeding time (PFA-100)	Other
Haemophilia A	N	↑	N	Factor VIII ↓
Haemophilia B	N	↑	N	Factor IX ↓
von Willebrand's disease	N	↑	↑	von Willebrand factor ↓ Factor VIII ↓ Abnormal platelet aggregation with ristocetin

Table 35.1 Coagulation changes in acquired disorders of coagulation.

	PT	APTT	TT	Platelets	Other
Liver disease	↑	↑	N/↑	↓	Dysfibrinogenaemia
DIC	↑	↑	↑	↓	FDP ↑ ±RBC fragments on blood film
Vitamin K deficiency	↑	↑ or N	N	N	
Massive transfusion	↑	↑	N	↓	
Oral anticoagulants	↑	↑	N	N	
Heparin	↑	↑	↑	N (rarely ↓)	Anti-Xa ↓

APTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; FDP, fibrin degradation products; N, normal; PT, prothrombin time; RBC, red blood cell; TT, thrombin time.

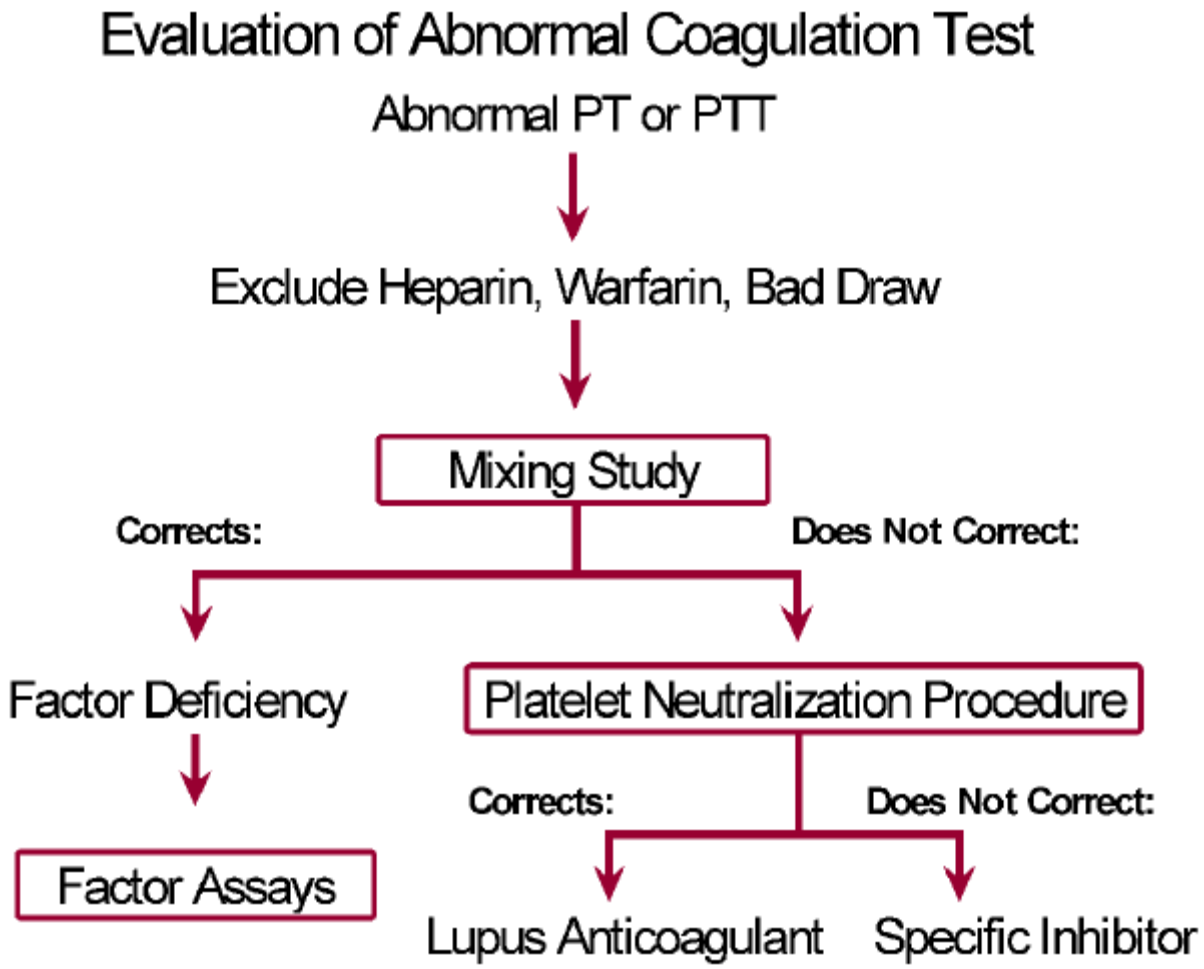


Figure 20–5 Evaluation of an abnormal coagulation test.

Anticoagulation

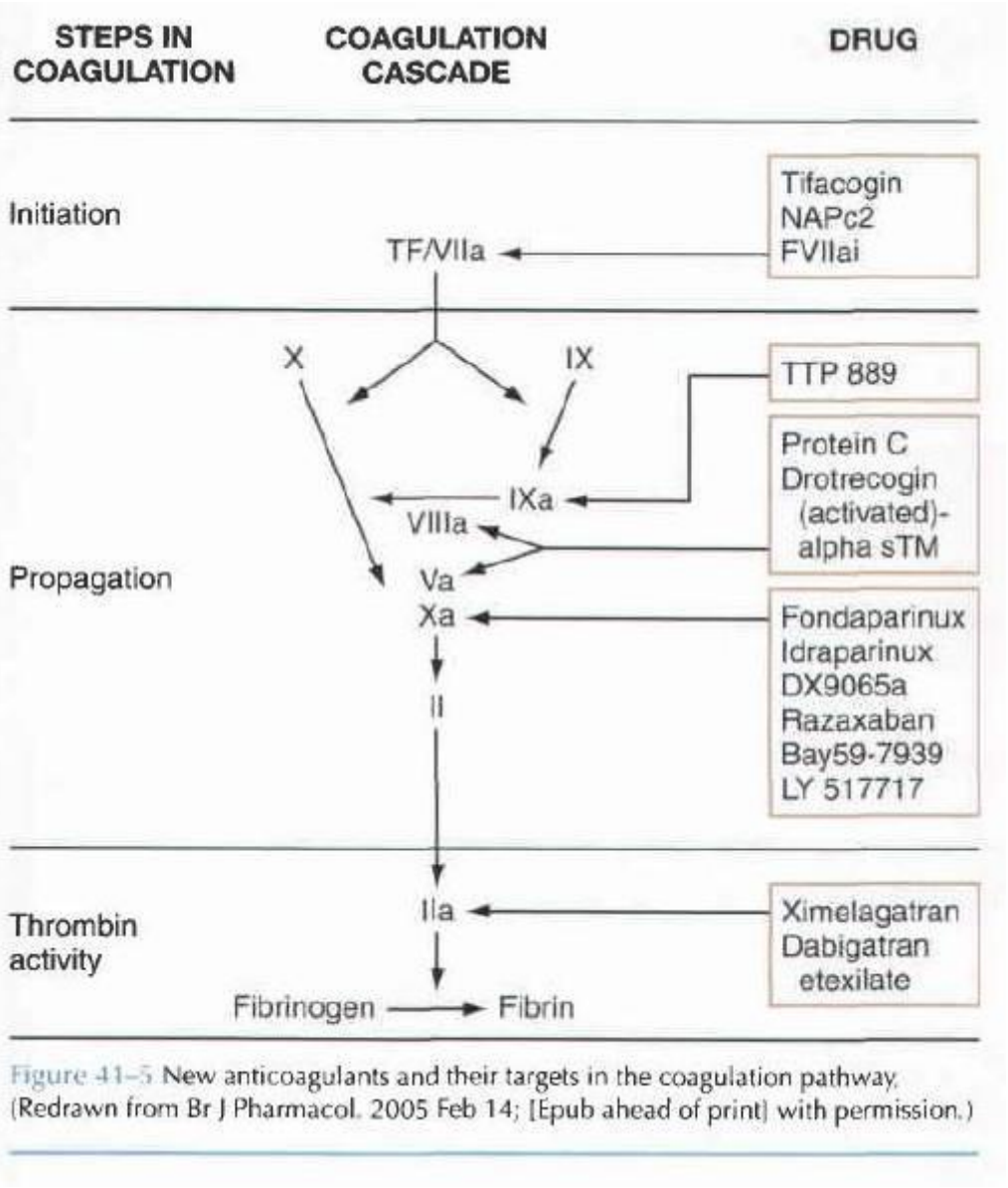


Figure 41–5 New anticoagulants and their targets in the coagulation pathway. (Redrawn from Br J Pharmacol. 2005 Feb 14; [Epub ahead of print] with permission.)

Overview of Hemostasis and Platelet Physiology

Summary Points

- Hemostasis depends on a system of checks and balances between thrombosis and hemorrhage that involve procoagulants and anticoagulants.
- The systems involved in hemostasis are the vascular system, platelets, coagulation system, and fibrinolytic system.
- Primary hemostasis is composed of platelet function and vasoconstriction.
- Secondary hemostasis is composed of fibrin clot formation and fibrin clot lysis.
- Platelet aggregation is mediated by von Willebrand's factor (vWF) and platelet glycoprotein Ib (GP1b).
- Platelets are small discoid cell fragments that are synthesized in the bone marrow and stimulated by the hormone thrombopoietin.
- There are four phases to platelet function at the site of injury: platelet adherence to collagen, platelet

aggregation, platelet granule release, and stabilization of the clot.

- Coagulation factors are produced in the liver with the exception of a portion of factor VIII, produced in the endothelial cells.
- The traditional coagulation pathway is divided into the intrinsic, extrinsic, and common pathways.
- The extrinsic pathway is monitored by the prothrombin time, while the intrinsic pathway is monitored by the partial thromboplastin time.
- The intrinsic pathway is initiated by factor XII and surface contact with the endothelial cells.
- Tissue factor pathway inhibitor is able to block the activity of the tissue factor: factor VII complex soon after it becomes active.
- Plasma fibrinogen activated by thrombin results in a stable fibrin clot.
- The key components of the fibrinolytic system are plasminogen, plasminogen activators, plasmin, fibrin, fibrin degradation products, and inhibitors of plasminogen and plasmin.
- Streptokinase, urokinase, and tissue plasminogen activator are activators of the plasmin-plasminogen system.
- Tissue plasminogen activator is available as a pharmacological product to break up pathologically formed clots.
- Serine protease inhibitors and the protein C pathway are the major physiologic inhibitors of coagulation.
- The kinin system is activated by factor XII and contributes to vascular permeability.
- The complement system once activated may contribute to the release of procoagulant material.

Quantitative and Qualitative Platelet Disorders

- A normal platelet count is 150 to 450 $\times 10^9$/L.
- Decreased platelet counts will lead to mucosal membrane bleeding such as gingival bleeding, epistaxis, purpura, and petechiae.
- Preanalytic variables that may lead to thrombocytopenia include improper mixing of tubes, improper anticoagulant used, and improper amount of sample collected.
- Acute idiopathic thrombocytopenia purpura is often a condition of children recovering from viral illness who show a dramatic drop in platelet count.
- Chronic idiopathic thrombocytopenia purpura occurs in adults as a result of an IgG antibody produced against platelets.
- Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are consumptive disorders of platelets.
- Individuals with TTP present with fever, a microangiopathic hemolytic anemia, neurological complications, thrombocytopenia, and renal failure.
- Individuals with HUS are predominantly children, with fever, bloody diarrhea, microangiopathic hemolytic anemia, thrombocytopenia, and renal failure.
- von Willebrand's disease (vWD) is a disorder of platelet adhesion in which von Willebrand factor is decreased or absent.
- vWD is the most common inherited qualitative platelet disorder, affecting 1% to 3% of the world's population.
- There are three primary types of vWD: type 1, type 2A, and type 3.
- Bernard Soulier syndrome is a platelet adhesion defect in which glycoprotein Ib is decreased or absent.
- Glanzmann's thrombasthenia is a defect of platelet aggregation that shows an absence of glycoprotein IIb/IIIa.
- Platelets from patients with vWD disease and Bernard Soulier syndrome will NOT aggregate with ristocetin.
- Aspirin impairs platelet function by interfering with the synthesis of thromboxane A_2, a potent platelet-aggregating agent.
- The platelet release function is impaired in the inherited disorders: Chediak-Higashi, Hermansky-Pudlak, Wiskott-Aldrich, gray platelet syndrome, and thrombocytopenia with absent radii syndrome.
- External conditions that alter platelet function include drugs, paraproteinemias, uremia, and the use of plasma expanders, like dextran.
- Skin, collagen, and blood vessels are essential elements in the hemostatic system.
- Any abnormality, inherited or acquired, in any one of these components of the vascular system will lead to mucosal bleeding such as purpura, petechiae, ecchymosis, or telangiectasia.

Defects of Plasma Clotting Factors

Summary Points

- Patients with recurrent bleeding episodes need to be evaluated for an inherited bleeding disorder.
- Bleeding comes under two main categories: open bleeds or closed bleeds.
- Plasma clotting factors need to maintain approximately 30% activity to achieve adequate clotting.
- The factor VIII molecule is carried into plasma by vWF.
- Hemophilias A and B are sex-linked recessive disorders.
- In hemophilia A, factor VIII is deficient; in hemophilia B, factor IX is deficient.
- Women are carriers of the defective hemophilia gene.
- From 15% to 20% of all hemophilia A individuals develop factor VIII inhibitors.
- Individuals with factor II, V, VII, and X deficiencies may have minimal bleeding.
- Prothrombin complex concentrate is used to correct deficiencies of factors II, VII, IX, and X.
- Prothrombin G20210A is a mutation of the prothrombin molecule.
- Factor V Leiden is a genetic mutation of the factor V molecule that predisposes to clotting episodes.
- Deficiencies of factors XI, XII, Fletcher, and Fitzgerald usually lead to increased thrombotic events.
- Factor XIII is unique among clotting factors because it is a transglutaminase; the other clotting factors are proteases.

- Individuals with hemophilia experience prolonged bleeding from minor wounds.
- Individuals with hemophilia may experience many types of bleeding including joint bleeding leading to hemarthrosis, hematomas, umbilical cord bleeding, or mucosal bleeds.
- The bleeding time is normal in hemophilia A and B patients; the aPTT is elevated.
- Current treatment for hemophilia individuals consists of recombinant factor products.
- Most individuals with hemophilia in the United States use factor concentrates prophylactically.
- Prophylactic infusion of factor concentrates has minimized the physical disabilities that may have occurred from unexpected bleeding episodes.

- An inherited deficiency of factor XIII may lead to poor wound healing and spontaneous abortions.
- Liver disease, renal disease, and autoimmune processes may lead to deficiencies in clotting factors that cause bleeding.
- Vitamin K is a fat-soluble vitamin necessary for the activation of factors II, VII, IX, and X.
- Vitamin K is available through the diet; small amounts are synthesized by normal intestinal flora.
- Newborns are vitamin K deficient and are given vitamin K at birth to avoid hemorrhagic disease of the newborn.
- If vitamin K is depleted, the PT and PTT will be prolonged.
- Coumadin, a therapeutic anticoagulant, is a vitamin K antagonist.

Fibrinogen, Thrombin, and the Fibrinolytic System

Summary Points

- Fibrinogen is the key substrate of the coagulation and the fibrinolytic system.
- Fibrinogen has the highest molecular weight of all of the clotting factors.
- Thrombin acts upon fibrinogen to convert it to fibrin.
- Fibrin is stabilized by factor XIII and calcium to become an insoluble clot.
- Plasminogen is converted to plasmin primarily through tissue plasminogen activator and then proceeds to destroy the fibrin clot.
- Afibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia are all inherited disorders of fibrinogen. Each of these may also be acquired disorders.
- Streptokinase is an exogenous fibrinolytic agent, produced when a bacterial cell product forms a complex with plasminogen.
- Naturally occurring inhibitors of fibrinolysis are plasminogen activator inhibitor 1 and alpha-2-antiplasmin.
- The byproducts of fibrinolysis are fibrin degradation products and D-dimers.
- Excess fibrin degradation products provide anticoagulant activity.

- D-dimers are produced from a cross-linked and stabilized fibrin clot.
- Excess D-dimers are an indication that clots have been formed and are being excessively lysed.
- Disseminated intravascular coagulation (DIC) is usually triggered by an underlying pathological event.
- In DIC patients will excessively clot or excessively bleed, or both.
- Laboratory results for a patient with acute DIC will show a prolonged PT and PTT, decreased fibrinogen and platelets, and increased fibrin degradation products and D-dimers.
- Treatment for DIC includes investigating and resolving the cause of the disorder and providing blood bank products as needed.

Introduction to Thrombosis and Anticoagulant Therapy

Summary Points

- Hypercoagulability refers to conditions that predispose an individual to thrombosis.
- Risk factors associated with hypercoagulability can be divided into those that are environmental, acquired, or inherited.
- Thrombosis is the formation of blood clots in the vasculature. Thrombosis can be arterial or venous.
- Arterial thrombosis is mainly composed of platelets with small amount of red cells and white cells, whereas venous thrombosis is composed of fibrin clot and red cells
- Thrombosis may result from vascular injury, platelet activation, coagulation activation, defect in fibrinolytic system, and defect in physiological inhibitors.
- Physiological thrombosis results from the body's natural response to vascular injury. It is localized and is formed to prevent excess blood loss.
- Pathological thrombosis includes deep venous thrombosis, arterial thrombosis, and pulmonary embolism. Pathological thrombosis may be caused by acquired or inherited conditions.
- Thromboembolism is formed when clot is dislodged from the origination site and filtered out in the pulmonary circulation.
- Physiological anticoagulant is plasma protein and includes antithrombin, heparin cofactor II, protein C, and protein S.
- Antithrombin is made in the liver. It inhibits factors IIa, IXa, Xa, XIa, and XIIa. Heparin increases the inhibitory action of antithrombin.
- Protein C is a vitamin K–dependent protein made in the liver. Protein C is activated by thrombin-thrombomodulin complex. Protein S is a cofactor for activation of protein C. Activated protein C deactivates factors Va and VIIIa.
- Inherited risk factors are associated with genetic mutations that result in deficiency of naturally occurring inhibitors such as protein C, protein S, or antithrombin; accumulation of procoagulant factors as in prothrombin G20210A; or clotting factor resistance to anticoagulant activities of physiological inhibitors as in activated protein C resistance.
- The majority (92%) of activated protein C resistance cases are inherited and are caused by mutation of factor V Arg506Gln, referred to as factor V Leiden.

- Acquired thrombotic disorders are associated with underlying diseases or drugs.
- Antiphospholipid syndrome is caused by antibodies against phospholipid-dependent coagulation assays such as aPTT, which was not corrected with 1:1 mix with normal plasma. The most common form of aPL antibodies are lupus anticoagulant (LA) and anticardiolipin (ACA).
- Laboratory tests for LA include aPTT or dRRVT; mixing studies, and confirmatory studies. Anticardiolipin antibodies are tested by ELISA.
- Heparin-induced thrombocytopenia (HIT) is an immune-mediated thrombotic complication associated with heparin therapy. The antibody is produced against heparin–platelet factor 4 complexes.
- Diagnostic tests for HIT include heparin-dependent platelet activation assays and detection of the antibody by ELISA.
- Antithrombotic drugs include antiplatelet drugs, anticoagulant drugs, and thrombolytic drugs.
- Aspirin is an antiplatelet drug that inhibits the cyclooxygenase (COX) enzyme and therefore prevents formation of thromboxane A_2 (TXA_2). TXA_2 is a potent platelet-activating substance released from the activated platelets.
- Heparin is a short-term anticoagulant drug. It is administered intravenously or intramuscularly.
- Heparin dosage is monitored by aPTT value to range from 1.5 to 2.5 times the mean of the laboratory control.
- Coumadin is a vitamin K antagonist drug that inhibits the vitamin K–dependent coagulation factors (II, VII, IX, and X).
- Coumadin is an oral anticoagulant that is administered as a long-term anticoagulant. It is monitored by PT/INR.
- Thrombolytic drugs include tPA, urokinase, and streptokinase.

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